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## The Capsid Structure of Human Bocaviruses

**Mario Mietzsch**[1], Mengxiao Luo[1], Shweta Kailasan[1], Maria Ilyas[1], Paul Chipman[1], Chen Xu[2], Kalle Kantola[3], Duncan Sousa[4], Robert McKenna[1], Maria Söderlund-Venermo[3], and Mavis Agbandje-McKenna[1]

[1]Department of Biochemistry and Molecular Biology, Center for Structural Biology, McKnight Brain Institute, College of Medicine, University of Florida, Gainesville, FL, USA; [2]Cryo-Electron Microscopy Facility, University of Massachusetts Medical School, Worcester, MA, USA; [3]Department of Virology, University of Helsinki, Helsinki, Finland; [4]Biological Science Imaging Resource, Department of Biological Sciences, Florida State University, Tallahassee, FL, USA

Human bocaviruses 1-4 (HBoV1-4) are associated with respiratory and gastrointestinal infections in young children causing pneumonia and/or diarrhea. The lack of treatment options or vaccination, and a limited understanding of their disease mechanisms demand the need to study these pathogens on a molecular and structural level for the development of therapeutics. Towards this end, the capsid structures of HBoV1-4 were determined to 2.7 – 2.9 Å resolution using cryo-electron microscopy and 3D image reconstruction. The HBoV capsids share common features with other parvoviruses, such as depressions at the icosahedral 2-fold and surrounding the 5-fold symmetry axes, protrusions surrounding the 3-fold, and a channel at the 5-fold axis. Despite these similarities, the major viral protein 3 (VP3) of the HBoVs contains loops with variable regions at their apexes conferring unique capsid surface topologies relative to other parvoviruses. Among the HBoVs the capsids display differences in surface loops that are potentially important for tissue tropism. Furthermore, unlike other parvoviruses, the bocavirus capsids possess additional densities at their VP N-terminus extending the 5-fold channel into the interior of the capsid. Redetermination of the HBoV capsid structures at low pH conditions (pH 2.6 and 5.5) to simulate the variable environment encountered during their replication cycle show disorder of the N-terminus density and modifications of select cysteine and histidine residues. These studies identified VP dynamics associated with capsid trafficking. Finally, efforts to identify the receptor for the HBoVs excluded terminal sialic acid, galactose, and heparan sulfate proteoglycan as host cell receptors. This study provides a structural framework to characterize the determinants of tissue tropism and HBoV capsid dynamics that could aid future development of anti-viral strategies to control human bocavirus infections.